

REMARKS

Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks. Claims 1-63 are pending, and claims 32-43 are under consideration. By the present amendment, claims 33, 37 and 42 are canceled. Claims 32, 34, 36, and 43 are amended, and claims 64 - 67 are added to more specifically recite certain aspects of the invention. Support for these amendments may be found throughout the specification and claims as originally filed, and it is urged that the amendments do not constitute new matter. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

Response to Restriction Requirement

Applicants respectfully request that the Examiner reconsider his decision regarding the restriction requirement and consider the claims of Group I, in addition to the elected claims of Group II. Applicants believe that consideration of both Groups I and II would not place a substantively greater burden on the Examiner.

Rejection Under 35 U.S.C. §102

Claims 32-35 and 39-41 stand rejected under 35 U.S.C. § 102(b) as anticipated by WO 99/13816 (Moynihan). More specifically, the Examiner asserts that Moynihan teaches liposomal formulations comprising various camptothecins in a precipitated form and that the drug-lipid ratios taught by Moynihan appear to fall within the claimed ratios.

Applicants respectfully traverse this basis of rejection and submit that Moynihan fails to anticipate the claimed invention, since Moynihan fails to disclose each element of the invention as presently claimed. Applicants note that independent claim 32 has been amended to require that the liposome comprises sphingomyelin and cholesterol. Since Moynihan fails to describe liposomes comprising sphingomyelin, Moynihan cannot anticipate claim 32 or claims 33-35 and 39-41 dependent therefrom. Applicants submit that the Examiner clearly recognized

the novelty of claims reciting liposomes comprising sphingomyelin and cholesterol, since he did not reject claim 43, which recites this limitation, under 35 U.S.C. §102(b).

Claims 32, 36 and 38-42 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,110,491 (Kirpotin). Specifically, the Examiner asserts that Kirpotin discloses liposomal compositions comprising various phospholipids, including sphingomyelin and cholesterol, wherein the active agent is in a precipitated form and wherein the active agent is any compound with ionizable groups, including antineoplastic agents, doxorubicin, vincristine, vinblastine and others.

Applicants respectfully traverse this basis of rejection and submit that Kirpotin fails to anticipate the claimed invention, since Kirpotin fails to disclose each element of the invention as presently claimed. Applicants note that independent claim 32 has been amended to require that the antineoplastic drug is a camptothecin, and claim 42 has been cancelled. As Kirpotin fails to describe active agents that are camptothecins, Kirpotin cannot anticipate claim 32 or claims 39-41 dependent therefrom. In addition, claim 36 has been amended to recite the limitation that the liposome comprises sphingomyelin and cholesterol at a ratio in the range of about 75/25 mol%/mol% sphingomyelin/cholesterol to about 35/50 mol %/mol% sphingomyelin/cholesterol. Support for this amendment is provided in the specification as filed, *e.g.*, page 8, lines 23-26. Since Kirpotin additionally fails to describe liposomes comprising sphingomyelin and cholesterol at a ratio within the recited range, Kirpotin does not anticipate claims 36 or claim 38 and newly added claims 64-66 dependent therefrom.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 102, in light of the above amendments and remarks.

Rejections Under 35 U.S.C. § 103(a)

Claims 37 and 39-41 stand rejected under 35 U.S.C. § 103(a) as unpatentable over WO 99/13816 (Moynihan). More specifically, the Examiner alleges that Moynihan teaches liposomal formulations comprising various camptothecins in a precipitated form and that even if the drug-lipid ratios taught by Moynihan fall outside the claimed ratios, it is obvious to one having ordinary skill in the art to vary the amounts of the active agents based upon the guidance provided by Kirpotin.

Applicants respectfully traverse this basis of rejection and submit that the Examiner fails to establish a *prima facie* case of obviousness in light of Moynihan. Claim 37 has been canceled without acquiescence to this basis of rejection. Applicants note that claims 39-41 are dependent from claim 32, which has been amended to recite liposomes comprising sphingomyelin and cholesterol. As described above, Moynihan fails to disclose liposomes comprising sphingomyelin and cholesterol. Accordingly, this reference does not teach or suggest each element of the claimed invention, as clearly required to establish a *prima facie* case of obviousness. *In re Royka*, 490 F.2d 981 (CCPA 1974).

Similarly, claims 37 and 39-43 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Kirpotin. Specifically, the Examiner asserts that Kirpotin discloses liposomal compositions wherein the active agent is in precipitated form and wherein the active agent can be any compound with ionizable groups. The Examiner further asserts that even if the drug-lipid ratios described in Kirpotin are different than those presently claimed, it would be obvious to one of ordinary skill in the art to vary the amounts of the active agents based upon the guidance provided by Kirpotin. The Action further alleges that Kirpotin discloses that sphingomyelin may be used in the liposomal compositions, but notes that Kirpotin does not specifically teach the use of camptothecins. Rather, the Action asserts that it would be obvious to one of ordinary skill in the art to use camptothecins, in light of Kirpotin's teachings regarding the use of ionizable drugs.

Applicants respectfully traverse this basis of rejection and submit that the Examiner fails to establish a *prima facie* case of obviousness in light of Kirpotin. Claims 37 and 42 have been canceled without acquiescence to this basis of rejection. Applicants note that claims 39-43 are dependent from claim 32, which has been amended to recite liposomes comprising sphingomyelin and cholesterol and having a camptothecin. As described above, Kirpotin fails to disclose liposomes having a camptothecin. Accordingly, this reference does not teach or suggest each element of the claimed invention, as clearly required to establish a *prima facie* case of obviousness. *In re Royka*, 490 F.2d 981 (CCPA 1974). Furthermore, Applicants disagree with the Examiner's position that Kirpotin's teachings regarding the use of ionizable drugs provide the suggestion or motivation required to render obvious the claimed liposomes, which specifically have a camptothecin. Nowhere does Kirpotin teach or suggest the use of a camptothecin. The teaching or suggestion to make a claimed combination must be found in the

prior art and not based upon the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed Cir. 1991). Accordingly, this basis of rejection appears to rest upon impermissible hindsight based upon the instant application's description of liposomes comprising a camptothecin.

In addition, Applicants submit that the teachings of Kirpotin would not motivate the skilled artisan to reach the presently claimed invention. On the contrary, Kirpotin actually teaches away from the presently claimed invention. Applicants note that the instant application describes the loading of an active agent into a liposome using a transmembrane pH or an ion gradient (page 9, lines 24-28). Accordingly, the addition of a proton or alkali metal-ion ionophore results in drug release from the liposomes. This is in contrast to Kirpotin, which specifies that the compound concentration in the liposomes is not reduced in the presence of a proton or alkali metal-ion ionophore (column 7, lines 4-29, and column 7, lines 43-53). Furthermore, Kirpotin teaches and claims methods of producing liposome-encapsulated compounds wherein the liposomes have substantially no transmembrane gradient of a hydrogen ion (see, *e.g.*, column 16, lines 49-50, and column 17, lines 26-28). In contrast, the instant application describes liposomal compositions wherein a transmembrane ion gradient is used to load the antineoplastic agent. Applicants submit that the skilled artisan would not be motivated to make or use liposomes having a transmembrane ion gradient, as described in the instant application, based upon the teachings of Kirpotin, which are directed to liposomes having substantially no transmembrane gradient. In light of these remarks, Applicants submit that the Examiner has not demonstrated that Kirpotin teaches each element of the claimed invention or would motivate the skilled artisan to reach the claimed invention and, therefore, has failed to establish a *prima facie* case of obviousness.

Claims 37 and 39-43 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kirpotin, further in view of U.S. Patent No. 6,355,268 (Slater *et al.*). The Action concedes that Kirpotin fails to specifically teach camptothecins but alleges that Slater *et al.* teaches that camptothecins are ionic and can be loaded using gradients as in Kirpotin. Therefore, the Action concludes that the use of antineoplastic agents in the liposomal compositions of Kirpotin would be obvious to one of ordinary skill in the art in light of the teachings of Slater *et al.*

Applicants respectfully traverse this basis of rejection and submit that the Action fails to establish a *prima facie* case of obviousness in light of the combination of Kirpotin and Slater *et al.* More specifically, the Examiner fails to establish any motivation to combine the cited references to achieve the claimed invention. As established by the courts and enunciated in the M.P.E.P., “[o]bviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention when there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” M.P.E.P., 8th Ed. § 2143.01. In the present case, neither reference teaches, suggests or would motivate the skilled artisan to combine the references to achieve the claimed invention. Rather, the two references each describe distinct methods of attempting to develop improved liposomal drug formulations. Specifically, Slater *et al.* teaches liposomes that include a vesicle-forming lipid derivatized with a hydrophilic polymer to increase drug retention and clinical efficacy (see, *e.g.*, Abstract and column 7, lines 37-38). Kirpotin describes an alternate approach at increasing drug retention, which involves encapsulating drug in a stable precipitated form. Neither reference provides any teaching or suggestion that these two methods could or should be combined to achieve the claimed invention drawn to liposomal formulations comprising sphingomyelin, cholesterol and precipitated camptothecins. Indeed, Kirpotin does not even contemplate the use of liposomes comprising camptothecins and, thus, provides absolutely no indication that liposomal camptothecin formulations comprising hydrophilic polymer-derivatized lipids would be advantageous. Slater *et al.* does not teach or even contemplate the precipitation of drugs within liposomes. Accordingly, the skilled artisan would have no motivation to combine these references to achieve the claimed invention.

In addition, Applicants submit that even assuming *arguendo* that each element of the claimed invention was taught by a cited reference, the cited combination of references fails to render the claimed invention obvious, since the references fail to provide the requisite teaching or suggestion of the desirability of combining the teachings of the references to reach the present invention. Applicants respectfully submit that the mere fact that the teachings of the prior art *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the prior art, does not make the resultant combination

prima facie obvious, as the prior art must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992)). Since neither of the cited references teach or suggest any advantage or desirability of modifying the teachings of the references to produce the claimed liposomal compositions, Applicants submit that the Action fails to establish a *prima facie* case of obviousness.

Furthermore, Applicants note that claim 37 is drawn to a liposomal composition comprising both free and precipitated antineoplastic agents, wherein said free and precipitated antineoplastic agents are different. The Examiner has provided no evidence that either Moynihan or Kirpotin teach or suggest liposomes comprising free and precipitated antineoplastic agent wherein the free and precipitated antineoplastic agents are different, and Slater *et al.* clearly fails to overcome this deficiency. Indeed, a careful review of these references reveals no indication that either contemplated the use of liposomes comprising two or more different antineoplastic agents, much less one free and a second precipitated antineoplastic agent. Accordingly, the skilled artisan would not be motivated by any of these references, alone or in combination, to produce the invention as recited in claim 37, and the invention is not obvious in light of either reference. Nonetheless, without acquiescence to this basis of rejection, claims 37 has been canceled without prejudice.

In light of the above amendments and remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

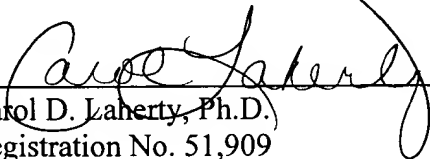
The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully request allowance of claims 32, 34-36, 38-41, 43, and 64-67. A good faith effort has been made to place this application in condition for allowance. However, should any further issue require attention, the Examiner is requested to contact the undersigned at (206) 622-4900.

Respectfully submitted,

Thomas D. Madden et al.

SEED Intellectual Property Law Group PLLC



Carol D. Laherty, Ph.D.
Registration No. 51,909

CDL:jto

Enclosure:
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

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